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TITLE: Targeting MRS-Defined Dominant Intraprostatic Lesions with Inverse-Planned High Dose Rate Brachytherapy

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14. ABSTRACT

A combination of MRI/MRSI is used to define the distribution of Dominant Intraprostatic Lesions (DIL) within the prostate. This information is used to perform dose escalation of the DIL without compromising the dose coverage of the prostate and the protection to the urethra, rectum, and bladder for prostate cancer patients treated with High Dose Rate (HDR) brachytherapy. The multi-image fusion process has been presented at national meetings during this period. The steps and criteria involved in the series of image fusions and in the planning and verification of the dose delivery process are presented. Information from one image data set to another in the series of MRS –> MRI –> CT <– CBCT can be accurately transferred and used for the planning and verification of the dose delivery during prostate HDR brachytherapy. Final CHR approval was obtained in 2008 and patient enrollment has begun. So far, 10 patients were treated with HDR brachytherapy with a DIL boost level ranging from 0 to 30%, using the previously established class solution for the set of parameters used by the inverse planning in order to boost the dominant intra-prostatic lesion (DIL) defined by MRI/MRSI. The DIL dose was significantly increased without any violation of standard dosimetric index requirements.

15. SUBJECT TERMS
MRI/MRSI , Dominant Intraprostatic Lesions (DIL), High Dose Rate (HDR) brachytherapy, multi-images fusion, dose escalation, prostate cancer.

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Table of Content

INTRODUCTION

Research Project Description

Men with prostate cancer, in particular those with advanced local disease, benefit from dose escalation. The main objective of the DOD-PC-030909 is to exploit the ability of Magnetic Resonance Imaging combined with Magnetic Resonance Spectroscopy imaging (MRI/MRSI) to identify cancer regions within the prostate and to target those regions with a higher tumor burden with higher dose without compromising the dose coverage of the prostate and the protection to the urethra, rectum and bladder for prostate cancer patients treated with HDR brachytherapy.

BODY

The feasibility of a comprehensive approach that incorporates MRI/MRSI (anatomical and functional imagining) into the HDR brachytherapy treatment planning has been demonstrated. Using the inverse planning program IPSA, dose escalation of target regions with a higher tumor burden can be performed without increasing the dose to critical normal structures. This is the first trial using both MR imaging and functional imaging MRSI for HDR brachytherapy planning.

Three main tasks were identified to fulfill the aims of this project:

Task 1: To determine the need for alignment and to establish alignment methods for MRI/MRSI data to HDR brachytherapy treatment planning MRI and CT images.

Task 2: To elaborate class solutions (a set of optimization constraints) appropriate for DIL boosts of the order of 150% of the prescribed dose and protection for the penile bulb and the neuro-vascular bundle valid for 90% of the cases.

Task 3: To perform feasibility and short-term measures of improved effectiveness and decreased side effects of performing the proposed treatment planning protocol in a small cohort of patients.

The status of the different tasks is as follow:

Task 1: **Completed**,
Task 2: **Completed**
Task 3: **In progress**

Information on Tasks 1 and 2 was provided in previous annual reports. Patient enrollment will continue. The information provided in this annual report supports the following: Task 3a. Determine how often the treatment planning method meets the goals of the treatment plan.

Patient enrollment and performing DIL boost (current period).

The period of performance has been extended for one year, until May 25th, 2011. Patient enrollment has been initiated in 2008 and the first HDR delivery with DIL boost was performed on September 2008**.** Fifteen patients were screened, and ten patients were treated with HDR so far. Eight of these patients had level 5 DIL, allowing DIL boost of at least 120-130%. So far, these results are as expected and very encouraging. The procedure is now well integrated

clinically and the brachytherapy team has been completely trained. We anticipate a smooth continuation of the protocol as patient enrollment proceeds. We believe the results of this research, once completed, will greatly impact the treatment of prostate cancer. The ability to provide a higher dose of radiation to regions of cancer within the prostate is expected to improve the disease free survival rate with no additional side effects.

During the current period, we have focused our activities on three aspects,

1- Evaluate the use of our Multi-Image fusion in a clinical setting
2- Perform DIL boost on enrolled patients.
3- Quarterly reports

1- Multi-Image Fusion (current period).

We have shown that information from one image data set to another in the series of MRS –> MRI -> CT <- CBCT can be accurately transferred and used for the planning and verification of the dose delivery during prostate HDR brachytherapy. This workflow illustrates the clinical benefit of image registration tools.

Studies have shown that greater control of localized prostatic tumors can be achieved with higher radiation doses. High Dose-Rate (HDR) brachytherapy can provide a focal dose escalation, and prior studies have shown that combined external beam radiation therapy (EBRT) and HDR yields favorable outcomes, particularly in patients with locally advanced disease. In our current HDR brachytherapy clinical protocol, a combination of magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI) is used to define Dominant Intraprostatic Lesions (DIL). This information is used to perform dose escalation of the DIL without compromising the dose coverage of the prostate nor the protection to the urethra, rectum, and bladder. There are two difficulties, however, inherent in this approach. The first is the merging of information from the staging MRI/MRSI exam with anatomic CT exam required for treatment planning; the second is the capacity of the treatment modality/ treatment planning system to deliver radiation doses in a precise fashion. Three imaging modalities, Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopic Imaging (MRSI), and Computed Tomography (CT) - are used at different steps during the process.

However, since the endorectal probe used for MRI/MRSI acquisition can induce significant prostatic compression and deformation, a non-rigid transformation is required to register accurately the probe-in MRSI data with the probe-out CT images used for treatment planning. We have developed and clinically implemented a new method combining rigid translations (for centroid alignment), rotations (to model the X axis rotation), and an in-plane non-rigid control-point based morphing method that utilizes a local weighted-mean transformation. This method was designed to be computationally inexpensive and easily implemented on the MATLAB (The Mathworks, Natick, MA) platform using built-in functions.

For each patient enrolled in the study, a pre-therapy staging MRI/MRS exam using an endorectal probe (i.e. probe in, or PI) were acquired and registered so that the MRSI-defined DIL was delineated on the anatomic MRI volume. A probe out axial MRI series (MRI-PO) was also acquired. Control point pairs at corresponding anatomic features on MRI-PI and MRI-PO series were chosen and used to determine the PI-PO transformation. This transformation algorithm was used to correlate spectroscopic data (MRSI-PI) to the MRI-PO data. Mutual Information was calculated to measure warping accuracy. On the HDR treatment day, the planning CT and the MRSI-PO were imported in the brachytherapy planning system and registered to each other. The prostate anatomy alone was used to guide the fusion. Target and

organs at risk were delineated on the CT while the DIL was contoured on the MRSI-PO using spectroscopic information. Catheters were then digitized, the plan was optimized using the inverse planning tool IPSA, with dose escalation to the DILs, while simultaneously treating the entire prostate without increasing the dose to surrounding normal tissues. The dose for the first fraction is then delivered.

The complete procedure was clinically integrated and has been used for the treatment of ten HDR patients with MRSI information. The data analysis is completed for six patients. For those six patients, the mean prostatic rotation induced by the coil was 20°±9°, and the mean gland volume was 27±14 cc. Urethra, peripheral zone margins, prostate boundaries, and various hyper / hypointense features on the images served as effective landmarks for the MRI-PI - MRI-PO fusion.

This makes information about the prostate cancer location routinely available, and allowing the use of inverse planning IPSA to boost dominant intraprostatic lesions during HDR brachytherapy, while preserving the prostate coverage and keeping the dose delivered to the organs at risk to the same level compared to an inverse planned dose distribution without DIL boost. Information from one image data set could be accurately transferred to another in the series of MRS → MRI → CT. This workflow was routinely used for the dose planning, including a DIL boost. This work illustrates the clinical benefit of image registration tools.

2- Perform DIL boost on enrolled patients

Patient enrollment has been initiated in 2008 and the first HDR delivery with DIL boost was performed on September 2008. During that period, we have screened 15 patients and 10 were enrolled and completed their HDR Brachytherapy. Five patients have completed the study.

The table below presents the dosimetric characteristics of the ten patients enrolled in the protocol that received HDR brachytherapy. Irrelevant of the DIL boost level, a plan must fulfill the RTOG-0321 dose criteria for target dose coverage $V100^{Prostate}$ > 90% and organ-at-risk dose sparing $V75^{Bladder}$ < 1 cc, $V75^{Rectum}$ <1 cc, $V125^{Urethra}$ <1 cc. As it can be seen, all dosimetric indices fulfill the limits used for a regular treatment. One patient in the cohort of ten patients did not have a level 5 MRS-defined DIL. Therefore, no boost was attempted on the patient. Boost levels from 20% (120% of the prescribed dose) to 50% were easily achieved. One patient received a 50% boost. **T**he DIL dose was significantly increased without any violation of standard dosimetric indices requirements.

DOSE DISTRIBUTION STATISTICAL ANALYSIS OF THE PATIENTS TREATED WITH HIGH DOSE RATE BRACHYTHERAPY

#	NAM	Firs	ID#	Prostate Volume (cc)	Prostate V100(%)	Prostate V150(%)	Urethra Vol(cc)	Urethra V120(cc)	Bladder V75(cc)	Rectum V75(cc)	DIL1 Volume(cc)	DIL2	DIL3	DIL Boost level	# DIL	Highest MRS Level
1	H.	M.	718	17.6	96.0	37.00	0.95	0.03	0.00	0.60	0.67			150	1	5
2	C.	K.	4351	23.3	97.3	29.50	0.88	0.15	0.00	0.90	1.47			130	1	5
3	H.	G.	9408	42.2	91.7	26.58	1.29	0.11	0.64	0.21	none			n/a	0	3
4	I.	R.	3238	35.8	95.8	35.70	1.10	0.20	0.10	0.50	0.80	1.40		130	2	5
5	O.	G.	9954	33.7	95.6	33.35	1.11	0.36	0.00	0.68	0.92	0.10		130	2	5
6	Y.	Z.	8583	34.8	92.5	32.02	0.96	0.24	0.50	1.00	6.33			125	1	5
7	G.	M.	4923	30.6	96.0	32.20	1.04	0.10	0.00	0.10	1.40	0.30	0.20	120	3	5
8	L.	D.	611	26.9	95.7	38.60	0.86	0.14	0.19	0.21	No MRS info			n/a	0	n/a
9	U.	S.	8214	75.3	93.4	32.03	1.59	0.03	0.45	0.80	0.75	0.33		130	2	5
10	G.	C.	5882	42.1	92.3	32.20	0.76	0.15	0.00	0.84	1.04	0.11		120	2	4

3- Quarterly reports

As per protocol, Both P.I., the study coordinator, our statistician and brachytherapy physicist, perform quarterly meetings since patient enrollment has begun. During our meetings, we review data, evaluate toxicity and discuss related topics, including patient recruitment. The report entitled "Patient Enrollment Status" includes the patient identifier, the screening date, the enrollment date and the patient conclusion status.

Patient Enrollment Status

PHASE I STUDY OF TARGETING DOMINANT INTRAPROSTATIC LESION USING FUNCTIONAL MR SPECTROSCOPY AND HIGH DOSE RATE BRACHYTHERAPY

Department of Defense Collaborative Research Trials

Date: ___June 3, 2010 __ Principal Investigators: Drs. Jean Pouliot and Joe I-Chow Hsu

CHR Study Number: H11386-24294 Study Coordinator: ___Tracy Diep___
Account and Fund: PC 03090 ZZ Account # 49178603
Grant Ending Period: June 30, 2011 ZZ visit Number 14459290

# of Pts.	Patient Identifier (AB123)	Screening Date (date checklist was completed)	Enrollment Date (date consent form was signed)	Patient Conclusion Status		
				Ongoing	Dropout (enter date)	Completed (enter date)
1	M. H. 0718	7/03/08	6/30/08	No- Study completed		10/01/2009
2	C. K. 4351	6/23/08	6/20/08	No- Study completed		11/19/2009
3	G. H. 9408	7/18/08	8/13/08	No- Study completed		12/03/2009
4	R. I. 5238	1/19/08	1/15/08	No- Study completed		05/13/2010
5	G.O. 9954	1/30/09	1/30/09	No-Study completed		04/8/2010
6	F.F. 8197	2/12/09	2/12/09	No – MD recommend alternative treatment		
7	G.H 6128	2/16/09	2/12/09	No- ineligible/ started hormone		
8	D.A.6117	2/26/09	Pending consultation 3/11/09	No – ineligible/ CT +metastatic disease		
9	R. S. 3230	3/16/09	Pending for CT/Bone scan 3/12	Possible metastases		
10	Z. Y. 8583	4/21/09	4/21/09	Yes		
11	M.G. 4923	9/17/09	9/2/09	Yes		
12	D.L. 0611	10/5/09	10/01/09	Yes		
13	E. P. 0523	1/25/10	1/25/10	No-ineligible/ PSA too high	01/28/10	
14	S. U. 8214	1/29/10	1/21/10	Yes		
15	C. G. 5882	3/3/10	3/1/10	Yes		

KEY RESEARCH ACCOMPLISHMENTS

- **An MRSI to MRI/CT alignment protocol**, developed to exploit the high specificity of combined MRI/MRSI for detecting and localizing prostate cancer within the prostate, allows the accurate transfer of this information to the planning images.
- **The accurate merging of MRSI to MRI/CT allows the use of inverse planning IPSA** to boost dominant intraprostatic lesions during HDR brachytherapy.
- **Boost levels of 120-150% of DIL can be easily achieved** on most patients while keeping the dose levels to organs at risk within the usual limits.

REPORTABLE OUTCOMES

Peer-reviewed Publications (Last year only)

- Reed G., Cunha J.A., Noworolski S.M., Kurhanewicz J., Vigneron D.B. , Hsu I.C., and Pouliot J., **Multi-image registrations and their role in inverse planned HDR prostate brachytherapy for dose escalation of DIL defined by combined MRI/MRSI**. Submitted to Med. Phys. May 2010.

Presentations at International Conferences

- Role of imaging at the different steps of HDR prostate brachytherapy, Australasian Brachytherapy Group - 19th ABG Annual Scientific Meeting, Melbourne Au, April 9, 2010.

- The Physics and Future developments of IPSA, McGill Univ. Dec 4th, 2009, Montreal, Canada.

Presentations at National Meetings

- Multi-Image Fusions and Their Role in Inverse Planned HDR Prostate Brachytherapy For Dose Escalation of DIL Defined by Combined MRI/MRSI, 30th Annual Meeting of American Brachytherapy Society, Toronto, May 30th, 2009.

- Interfraction Adaptive Strategy for Multiple Lumen HDR Brachytherapy, Essentials in Brachytherapy, Scottsdale, Az, May 2nd, 2009.

CONCLUSION

An MRSI to MRI/CT alignment protocol was previously developed to exploit the high specificity of combined MRI/MRSI for detecting and localizing prostate cancer within the prostate, and to accurately transfer this information to the planning images. This information from one image data set can be accurately transferred to another in the series of MRS -> MRI -> CT. This workflow is now routinely used in clinic for the HDR brachytherapy dose planning, including a DIL boost. This makes information about the prostate cancer location routinely available, and allowing the use of inverse planning IPSA to boost dominant intraprostatic lesions during HDR brachytherapy, while preserving the prostate coverage and keeping the dose delivered to the organs at risk to the same level compared to an inverse planned dose distribution without DIL boost. This work illustrates the clinical benefit of accurate and consistent image registration tools, combined with inverse planning.

The screening and enrollment of patients in the study continues. Although the enrollment rate is slow, the workflow procedure is now well integrated in clinic. Boost levels of 120-150% of DIL can be easily achieved on most patients while keeping the dose levels to organs at risk within the usual limits.

APPENDICES

Abstracts

1- MULTI-IMAGE FUSIONS AND THEIR ROLE IN INVERSE PLANNED HDR PROSTATE BRACHYTHERAPY FOR DOSE ESCALATION OF DIL DEFINED BY COMBINED MRI/MRSI, Jean Pouliot, Adam Cunha, Galen Reed[2], Sue Noworolski, John Kurhanewicz, and I-Chow Hsu. ABS Annual Meeting, Toronto, May 30th, 2009. (Abstract included in appendice)

2- USING THE RIGHT IMAGE AT THE RIGHT TIME IN PLANNING, DELIVERY AND VERIFICATION OF INVERSE PLANNED HDR PROSTATE BRACHYTHERAPY,
J. Pouliot, Australasian Brachytherapy Group - 19th ABG Annual Scientific Meeting, Melbourne Au, April 9, 2010. (Abstract included in appendice)

3- MULTI-IMAGE REGISTRATIONS AND THEIR ROLE IN INVERSE PLANNED HDR PROSTATE BRACHYTHERAPY FOR DOSE ESCALATION OF DOMINANT INTRAPROSTATIC LESION DEFINED BY COMBINED MRI/MRSI,
J. Pouliot, DOD-IMPACT meeting, 2011.

Publication (last year only)

Reed G., Cunha J.A., Noworolski S.M., Kurhanewicz J., Vigneron D.B. , Hsu I.C., and Pouliot J., **Multi-image registrations and their role in inverse planned HDR prostate brachytherapy for dose escalation of DIL defined by combined MRI/MRSI.** Submitted to Med. Phys., May 2010.

ABSTRACT 1

American Brachytherapy Society (ABS) Annual Meeting,
Toronto, May 30th, 2009.

MULTI-IMAGE FUSIONS AND THEIR ROLE IN INVERSE PLANNED HDR PROSTATE BRACHYTHERAPY FOR DOSE ESCALATION OF DIL DEFINED BY COMBINED MRI/MRSI

Jean Pouliot[1], Adam Cunha[1], Galen Reed[2], Sue Noworolski[2], John Kurhanewicz[2], and I-Chow Hsu[2].

1- Department of Radiation Oncology, University of California San Francisco
2- Department of Radiology and biomedical imaging, University of California San Francisco

Purpose: We have recently initiated a clinical protocol where a combination of MRI/MRSI is used to define the distribution of Dominant Intraprostatic Lesions (DIL) within the prostate. This information is used to perform dose escalation of the DIL without compromising the dose coverage of the prostate and the protection to the urethra, rectum, and bladder for prostate cancer patients treated with HDR brachytherapy. The objective of this work is to present the steps and criteria involved in the series of image fusion involved in the planning and verification of the dose delivery process.

Materials and Methods: Four imaging modalities (MRI, MRS, CT and CBCT) are used at different steps during the planning and dose delivery of HDR brachytherapy. A few weeks before radiation therapy, MRI and MRS with probe in (pi) are acquired and combined into one MRSI-pi data set. A probe out MRI (MRI-po) is also acquired. Select control point pairs for matching anatomic features on MRI-pi and MRI-po series are used to determine the pi-po transformation. The alignment and morphing of the 1H Spectroscopic data MRSI-pi is matched to the MRI-po data using this transformation, including translation, rotation and a morphing algorithm. Overlap between the probe-in and probe-out masks is calculated. On the HDR treatment day, the planning CT and the MRSI-po are imported in the brachytherapy planning system and registered. The prostate anatomy alone is used to guide the fusion. Target and organs at risk are delineated on CT while the DIL is contoured on the MRSI-po. Catheters are then digitized, the plan is optimized using IPSA, and the dose for the first fraction is delivered. On the next day after the implant, prior to the dose delivery of the second fraction, a Cone-Beam CT (CBCT) is acquired and fused with the planning CT of the precedent day to verify the correct positioning of the catheters relative to the anatomy. This fusion is performed using the three implanted fiducial gold markers.

Results: For the MRI-pi – MRI-po fusion, urethra, peripheral zone margins, prostate boundaries, and various spots of hyper / hypointensity are effective landmarks. The prostate rotation angle induced by the endorectal coil is determined by the margin of the central zone / peripheral zone as seen on a sagittal series. This angle is typically non-negligible (20 – 30 degrees). At least 12 point pairs, selected more from regions with high deformation (such as the posterior aspect of the peripheral zone) and regions of MRI-pi abnormality are required to ensure accurate morphing. The visual inspection as well as the computed overlap serve as an effective diagnostic of the morphing. When control points are misplaced, the masks appear lopsided or wildly distorted. On the day of the first fraction, the MRSI-CT fusion followed by the delineation of the DIL adds less than thirty minutes to the entire planning process. For the second fraction, the visualization of the fused CT-CBCT images, with CBCT displayed in inverse video, allows for a rapid and precise evaluation of the correct positioning of the catheters.

Conclusion: Information from one image data set to another in the series of MRS –> MRI -> CT <- CBCT can be accurately transferred and used for the planning and verification of the dose delivery during prostate HDR brachytherapy. This workflow illustrates the clinical benefit of image registration tools.

This work was supported in part by Nucletron Corporation and from the DOD – W81XWH-04-1-0262 contract.

ABSTRACT 2

Australasian Brachytherapy Group - 19th ABG Annual Scientific Meeting,
Melbourne, Au, April 9, 2010.

Using the right image at the right time in planning, delivery and verification of inverse planned HDR prostate brachytherapy.

Jean Pouliot
Department of Radiation Oncology, University of California San Francisco

Using two studies recently completed, this presentation will focus on the role of imaging at the different steps of HDR prostate brachytherapy. MR-spectroscopy combined with CT for better dose planning and targeting, and CBCT to verify the integrity of the implant at each fraction and evaluate the dosimetric impact of catheter displacements.
- Study 1- Multi-image fusions and their role in inverse planned HDR prostate brachytherapy for dose escalation of DIL defined by combined MRI/MRSI.
- Study 2- An Inter-fraction Adaptive Strategy for High-Dose Rate Prostate Brachytherapy: Clinical application of the HDR BrachySuite equipped with CBCT.

ABSTRACT 3

To be submitted to DOD-IMPaCT: Innovative Minds in Prostate Cancer Research Today Conference 2011

Multi-Image Registrations and Their Role In Inverse Planned HDR Prostate Brachytherapy for Dose Escalation of Dominant Intraprostatic Lesion Defined by Combined MRI/MRSI,

J. Pouliot, Adam Cunha[1], Galen Reed[2], Sue Noworolski[2], John Kurhanewicz[2], and I-Chow Hsu[2].
1- Department of Radiation Oncology, University of California San Francisco
2- Department of Radiology and biomedical imaging, University of California San Francisco

Abstract not available yet.

Publication (submitted to Med. Phys.)

MULTI-IMAGE REGISTRATIONS AND THEIR ROLE IN INVERSE PLANNED HDR PROSTATE BRACHYTHERAPY FOR DOSE ESCALATION OF DIL DEFINED BY COMBINED MRI/MRSI

Galen Reed[1,3] , J. Adam Cunha[2], Susan M. Noworolski[1,3] ,
John Kurhanewicz[1,3] , Daniel B. Vigneron[1,3] , I-Chow Hsu[2], and Jean Pouliot[1,3]

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These results were presented at the American Brachytherapy Society Annual Meeting - 2009. This work was supported by DOD Grant, IDPCRP-DAMD17-PC02 (W81XWH-04-1-0262), NIH Grants RO1 CA79980, RO1 CA59897 and RO1 CA11129.

Introduction

Studies have shown that greater control of localized prostatic tumors can be achieved with higher radiation doses [1-3]. High Dose-Rate (HDR) brachytherapy can provide a focal dose escalation, and prior studies have shown that combined external beam radiation therapy (EBRT) and HDR yields favorable outcomes, particularly in patients with locally advanced disease [4-6]. We have recently initiated a HDR brachytherapy clinical protocol in which a combination of magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI) is used to define Dominant Intraprostatic Lesions (DIL). This information is used to perform dose escalation of the DIL without compromising the dose coverage of the prostate nor the protection to the urethra, rectum, and bladder. There are two difficulties, however, inherent in this approach. The first is the merging of information from the staging MRI/MRSI exam with anatomic CT exam required for treatment planning; the second is the capacity of the treatment modality/ treatment planning system to deliver radiation doses in a precise fashion. Three imaging modalities Ð Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopic Imaging (MRSI), and Computed Tomography (CT) - are used at different steps during the process.

The combined MRI / MRSI exam has been shown to be an effective method of detecting and localizing intraprostatic lesions [7-10]. The high sensitivity and specificity yielded by this exam has demonstrated great utility in focal treatment via ^{125}I brachytherapy implants [11] and combined HDR/EBRT [12, 13]. However, since the endorectal probe used for MRI/MRSI acquisition can induce significant prostatic compression and deformation, a non-rigid transformation is required to register accurately the probe-in MRSI data with the probe-out CT images used for treatment planning. To model this deformation, prior studies have implemented finite-element based biomechanical simulations [14, 15], elastic spline deformation [16], thin plate spline deformation [16-19], symmetric forces algorithms [20], Newton-Ralphson algorithms [21], and in-plane linear scaling assuming constant volume [11]. Kim et al [22] showed that the inflatable endorectal coil-induced deformation is negligible in the Z dimension since the induced distortions are less than the axial slice thickness of 3mm. The same study also showed that the coil induces a non-negligible rotation about the X (right/left) axis. The goal of this study was to develop and implement a new method combining rigid translations (for centroid alignment), rotations (to model the X axis rotation), and an in-plane non-rigid control-point based morphing method that utilizes a local weighted-mean transformation [23]. This method was designed to be computationally inexpensive and easily implemented on the MATLAB (The Mathworks, Natick, MA) platform using built-in functions. In this paper, we present the steps and criteria involved in the series of image registrations used clinically during the planning of the dose delivery process.

Methods and Materials

For each patient enrolled in the study, a pre-therapy staging MRI/MRS exam using an endorectal probe (i.e. probe in, or PI) were acquired and registered so that the MRSI-defined DIL was delineated on the anatomic MRI volume. A probe out axial MRI series (MRI-PO) was also acquired. Control point pairs at corresponding anatomic features on MRI-PI and MRI-PO series were chosen and used to determine the PI-PO transformation. This transformation algorithm was used to correlate spectroscopic data (MRSI-PI) to the MRI-PO data. Mutual Information was calculated to measure warping accuracy. On the HDR treatment day, the planning CT and the MRSI-PO were imported in the brachytherapy planning system and registered to each other. The prostate anatomy alone was used to guide the fusion. Target and organs at risk were delineated on the CT while the DIL was contoured on the MRSI-PO using spectroscopic information. Catheters were then digitized, the plan was optimized using the inverse planning tool IPSA[13], with dose escalation to the DILs, while simultaneously treating the entire prostate without increasing the dose to surrounding normal tissues. The dose for the first fraction was then delivered.

Subjects

Six patients were scanned and subsequently treated with this protocol. Their age ranged from 44 to 80 years old (mean 61). All patients had biopsy-proven Gleason 3+3 disease, and five of six of the subjects showed Gleason 3+4 pattern in histological analysis. The mean PSA measurement for all subjects was 8.8 ng/mL (ranging from 4.3 ng/mL to 19.5 ng/mL). Written informed consent was obtained for all subjects

following a protocol approved by the UCSF Committee of Human Research.

Identification of DIL with MRS and MRI

MR imaging was acquired with GE 3T and 1.5T SIGNA scanners (GE Medical Systems, Milwaukee, WI) using body-coil excitation. The GE 8-channel pelvic phased array and Medrad endorectal coil (Medrad, Pittsburgh, PA) were used for signal reception. Axial T1-weighted images were acquired with TR/TE = 600/12. FSE T2-weighted images were acquired (TR/TE = 6000/102, 14cm FOV, 256×256 matrix) in the axial, sagittal, and coronal planes. Images were and spectroscopic data were first acquired with the endorectal probe inserted. The probe was then removed, and an additional sagittal locator and an axial FSE T2 image data set were then acquired using the pelvic phased array for signal reception.

Spectroscopic data was acquired using a specialized prostate 3D MRSI sequence [24] (if 1.5T cases are included, [25, 26]) with a 12×8×8 grid yielding 0.157cc voxels. Water and lipid suppression was achieved using dual-band spectral spatial pulses [27]. Very-selective spatial saturation (VSS) pulses were used to suppress periprostatic lipids [28, 29]. In each voxel 1024 points were acquired over a 1000Hz frequency domain. The k-space data was zero-filled in the superior/inferior and anterior/posterior dimensions to a final array size of 12×16×16. The spectral data was then apodized with a 3Hz Gaussian filter, Fourier transformed, baseline corrected, frequency aligned, and peaks numerically-integrated. Numerical integration of each of the prostate metabolite peaks (choline, creatine, and citrate) and the suppressed water peak was performed using the known frequency positions of each of these peaks [30].

Spectroscopic voxels were classified using the standardized scoring system proposed by Jung *et al* [31] where 1 = definitely normal, 2 = probably normal, 3 = equivocal, 4 = probably abnormal, and 5 = definitely abnormal. After the generation of these scores by a trained reader, grayscale images of these scores were created at the MRSI resolution so that the suspicious voxels could be delineated by color on the high resolution T2 volume (Figure 1).

Warping the MRSI Grid

a. Rotation

Sagittal images acquired with and without the endorectal probe were analyzed to determine the rotation of the prostate about the R/L axis induced by the probe. The prostatic alignment of each series is determined by the margin of the peripheral zone and central zone as shown in Figure 2. The image volumes are rotated by the net rotation angle $\theta_{probein}$-$\theta_{probeout}$ using tri-linear interpolation.

b. Translation

Prostatic margins were then hand-drawn on both the axial probe-out volume and the rotated axial probe-in volume. Masks were drawn on the ten to twelve corresponding slices in each volume. The centroids of the masks are calculated, and the rotated axial probe-in volumes were translated so their centroids line up with the centroid of the probe-out volume. The net translation applied is $\Delta R = R_{CI} - R_{CO} + C_O - C_I$, where R_{CI} and R_{CO} are the centers and C_I and C_O are the prostate centroids of the probe-in and probe-out volumes respectively.

c. MR Morphing Procedures

After the rotation and translations are applied, a non-rigid deformation was then applied to model the prostatic deformation induced by the endorectal coil. To model this deformation, the probe-in and probe-out T_2 imaging series were compared slice-wise. In each slice, control point pairs were assigned to matching anatomical landmarks within the prostate (Figure 3). The control point locations were assigned using the MATLAB control point selection tool . These point pairs were then used to define a local weighted-mean [23] PI-PO transformation. This non-rigid transformation placed higher weighting on image regions with a higher control point density. Therefore, the reader could apply more control points onto regions where higher accuracy was required with the registration. Examples are regions of higher prostatic compression (the posterior aspect) and regions of suspected malignancy. The transformation was applied to the MRI-PI volume (to calculate morphing accuracy) and to the MRSI-PI data. Finally, the MRSI-PI data (after rotation, translation, and deformation) were delineated on the probe-out T2 volume.

Mutual Information *MI* was calculated between the MRI-PO images and both the warped and non-warped MRI-PI images after rotations and translations were applied. This value was calculated similar to previous works [32-34] as

$$MI(r,f) = \sum_{r,f} p_{RF}(r,f)\log\left(\frac{p_{RF}(r,f)}{p_R(r)p_F(f)}\right), \quad (1)$$

where $p_{RF}(r,f)$ is the joint probability of the reference (probe-out) and floating (probe-in) images, and $p_R(r)$ and $p_F(f)$ are their corresponding marginal probabilities. MI was calculated only in the smallest-fitting rectangular boundary around the hand-drawn mask for each slice so that the erroneous morphing in the extra-prostatic regions (where no control points are placed) does not excessively sway the metric.

Target delineation for dose planning optimization

a. MRSI - Planning CT registration

On the HDR treatment day, a CT scan with 3 mm slice thickness was acquired immediately after the patient recovered from the implant procedure. The imaging volume was selected to zoom in on the prostate and was limited superiorly to include the bladder and inferiorly to visualize all the catheters down to the perineum. The planning CT and the MRSI-PO were imported in the brachytherapy planning system (OncentraBrachy™, Nucletron) , and a rigid body registration was obtained. The prostate anatomy alone was used to guide the fusion, since the prostatic position can vary with respect to extra-prostatic landmarks. Typically, 3 pair-points were defined: two by the urethra in the base and apex areas, and a third one more lateral to the prostate in the median plane. Target and organs at risk were delineated on the CT while the DIL(s) was (were) contoured on the MRSI-PO using spectroscopic information. Catheters were then digitized, the plan was optimized using IPSA, and the dose for the first fraction was delivered.

b. Definition of volumes of interest

Clinical target volumes (prostate) and organs at risk (urethra, bladder, rectum and bulb) were contoured on each CT slice (Figure 5a). The DIL, defined as spectroscopic voxel levels 4 or 5, were manually contoured on the CT, but the transparency level was adjusted to make the MRS information visible on the CT (Figure 5b). After the catheters were digitized on the CT, all information requested for the optimization of the dose distribution was available (Figure 6).

c. Dose optimization with Inverse planning IPSA

The inverse planning optimization algorithm was then used to increase the dose delivered to the dominant intra-prostatic lesions defined by MRI/MRSI while providing the usual dose coverage of the prostate and the protection to the urethra, rectum, bulb and bladder.

A class solution was previously developed [12] for dose escalation of a DIL defined by combined MRI/MRSI in inverse planned HDR prostate brachytherapy. Using the class solution, a certain level of DIL-boost was feasible for the majority of patients under the RTOG-0321 dosimetric requirements depending on rectal and bladder doses. The class solution in inverse planned HDR prostate brachytherapy for dose escalation of a DIL defined by combined MRI/MRSI is an excellent starting point to explore a customized set of dose constraints to obtain a satisfactory treatment plan for each patient in the ongoing protocol.

Results

The complete procedure was clinically integrated and has been used for the treatment of six HDR patients with MRSI information. Out of the six patients scanned, the mean prostatic rotation induced by the coil was $20^{\circ} \pm 9^{\circ}$, and the mean gland volume was 27±14 cc. Urethra, peripheral zone margins, prostate boundaries, and various hyper / hypointense features on the images served as effective landmarks for the MRI-PI - MRI-PO fusion (figure 3). At least 12 point pairs - selected primarily from regions with high deformation, such as the posterior aspect of the peripheral zone, and regions of spectroscopic

abnormality - are required as inputs to the MATLAB image transformation function. Visual inspection as well as the computed *MI* (Table 1) served as effective diagnostics of the morphing. *MI* showed a 25%±13% increase for the six patients. A paired t-test showed this improvement to be significant (p=0.0071).

On the day of the first fraction, performing the MRSI-CT fusion was followed by the delineation of the DIL, adding less than fifteen minutes to the entire planning process. The 3 pair-points registration procedure is considered valid when the sum of squared distances between each pair-point is less than 2 mm. A careful visual inspection of the fusion in the prostate area is also performed.

Conclusion

An MRSI to MRI/CT alignment protocol was developed to exploit the high specificity of combined MRI/MRSI for detecting and localizing prostate cancer within the prostate, and to accurately transfer this information to the planning images. This makes information about the prostate cancer location routinely available, and allowing the use of inverse planning IPSA to boost dominant intraprostatic lesions during HDR brachytherapy, while preserving the prostate coverage and keeping the dose delivered to the organs at risk to the same level compared to an inverse planned dose distribution without DIL boost. Information from one image data set could be accurately transferred to another in the series of MRS → MRI → CT. This workflow was routinely used for the dose planning, including a DIL boost. This work illustrates the clinical benefit of image registration tools.

Table 1: Quantification of Morphing Accuracy

patient	n slices	gland vol [cc]	X-axis angle [deg]	MI^{*}_{pre}	MI^{*}_{post}	p^{**}_{MI}	% improvement ***
1	9	16	15	0.3885	0.5327	0.0003	38
2	7	32	29	0.1912	0.2549	0.2141	41
3	11	54	5	0.4094	0.5075	0.0358	29
4	9	19	24	0.5009	0.5599	0.0263	12
5	9	22	24	0.2767	0.3006	0.4688	11
6	8	18	20	0.4080	0.4829	0.0071	19

* mean of all slices
** calculated between the pre and post morphing on all slices (intra-patient)
** calculated as the mean of the % improvement for each slice

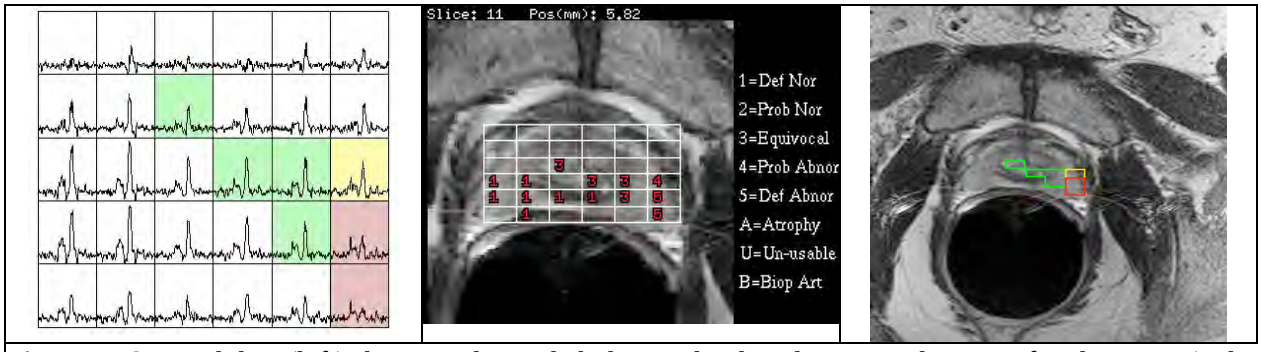

Figure 1: Spectral data (left) showing elevated choline and reduced citrate indicative of malignancy (red voxels). The center image shows the voxel classifications described by Jung *et al*, and the right image shows the suspicious regions delineated on the T2 image

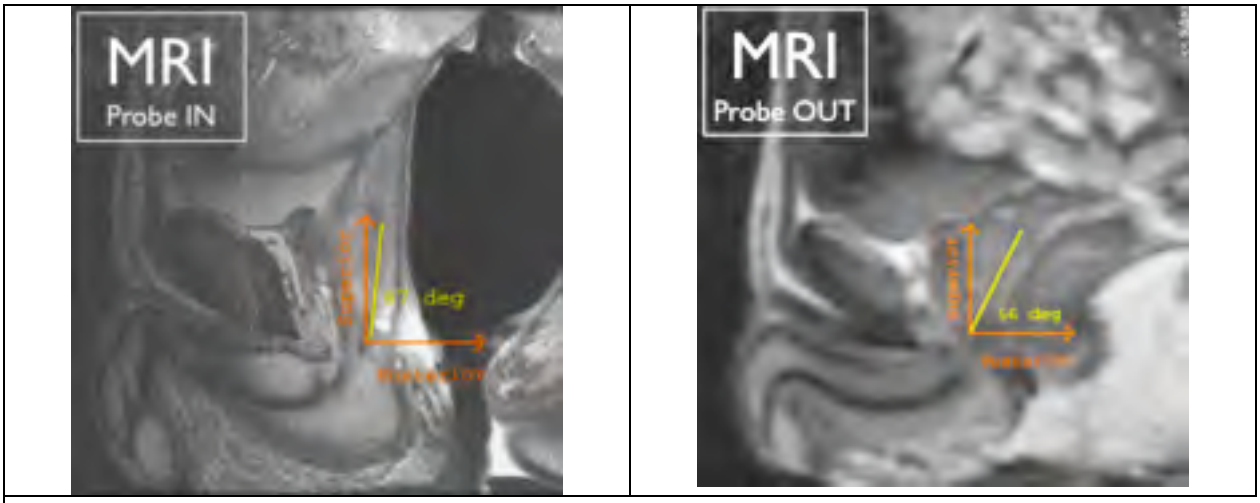

Figure 2: Mid-sagittal MR images showing the prostatic rotation induced by the endorectal coil. The angles were measured between the Y-axis and the peripheral zone / central zone margin.

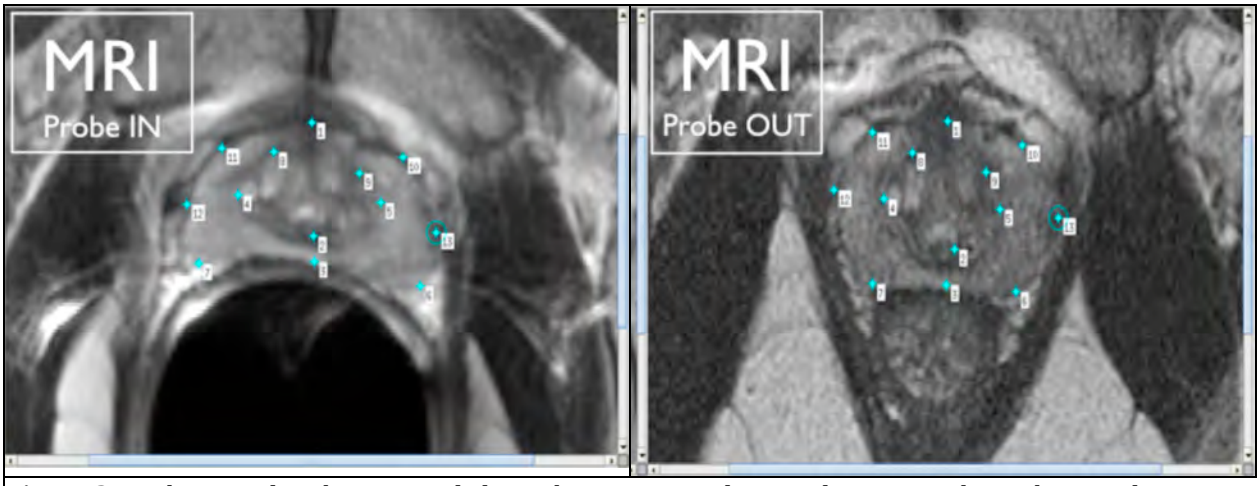

Figure 3: Probe-in and probe-out axial slices showing control point placement. The probe-in volume is rotated by the prostatic angle so the slices are assumed to be coplanar. Despite the lower SNR on the probe-out image, numerous landmarks are still identifiable on both images.

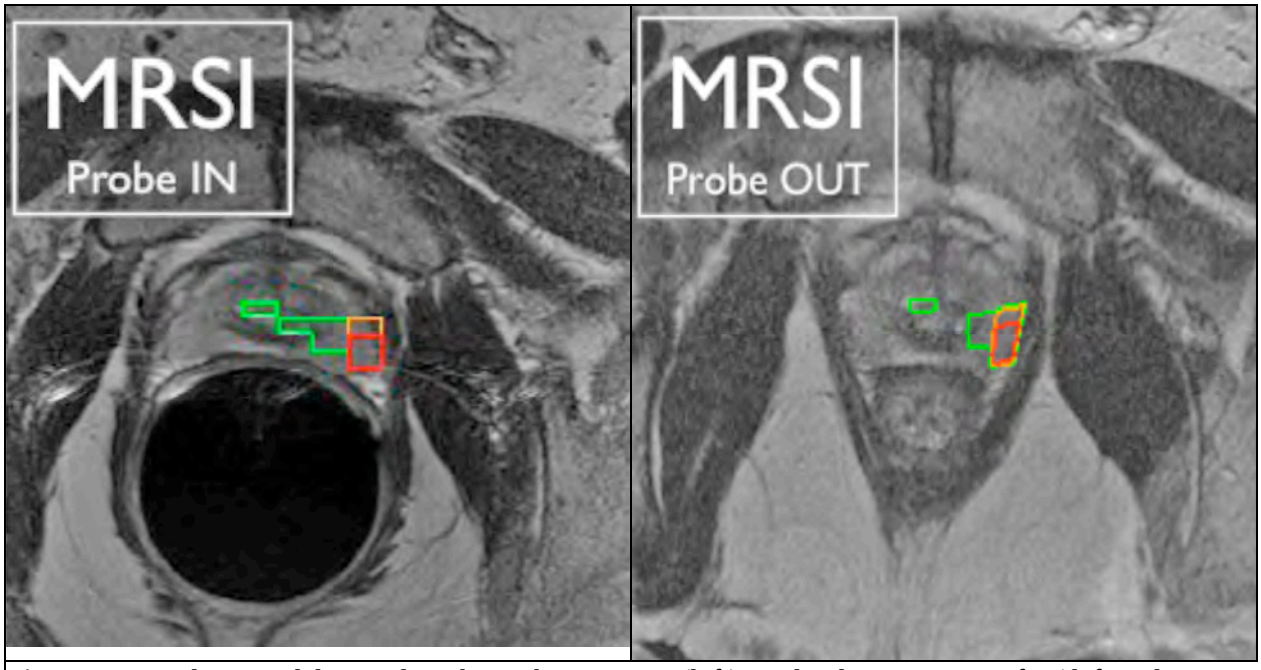

Figure 4: Voxel scores delineated on the probe-in image (left). Red indicates scores of 5 (definitely abnormal), orange indicates 4 (likely abnormal), and green indicates 3 (equivocal.). The right shows the rotated, translated, and warped voxel scores delineated on the probe-out image.

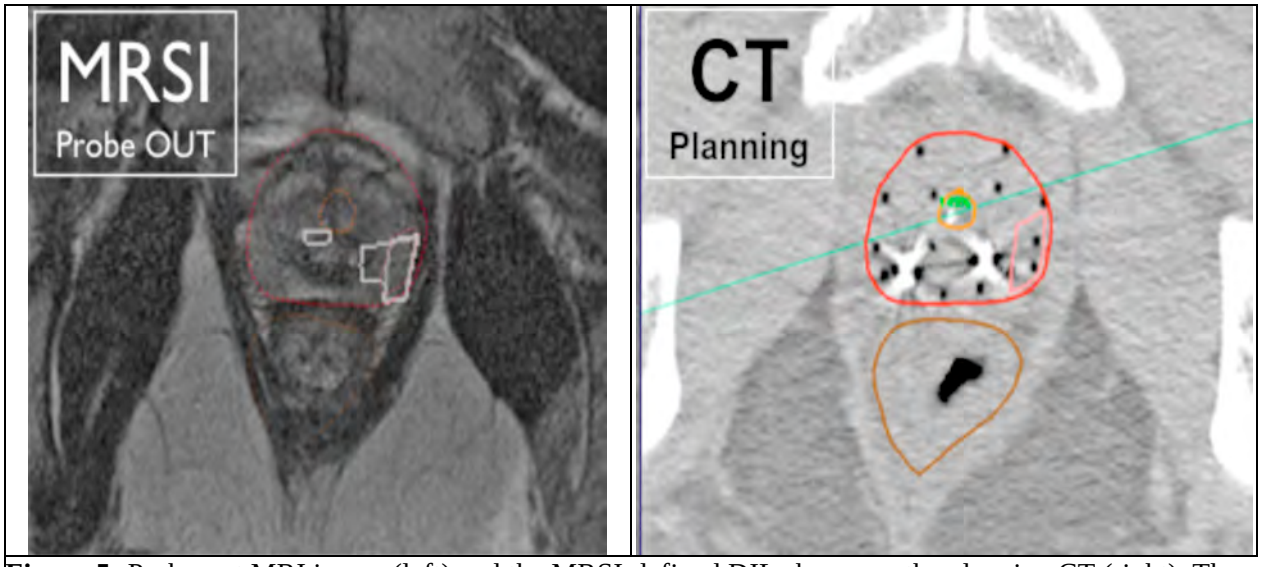

Figure 5: Probe-out MRI image (left) and the MRSI-defined DIL shown on the planning CT (right). The red contour indicates the prostatic margin, green indicates the urethra, brown indicates the rectum, and the pink contour delineates the MRSI-defined DIL.

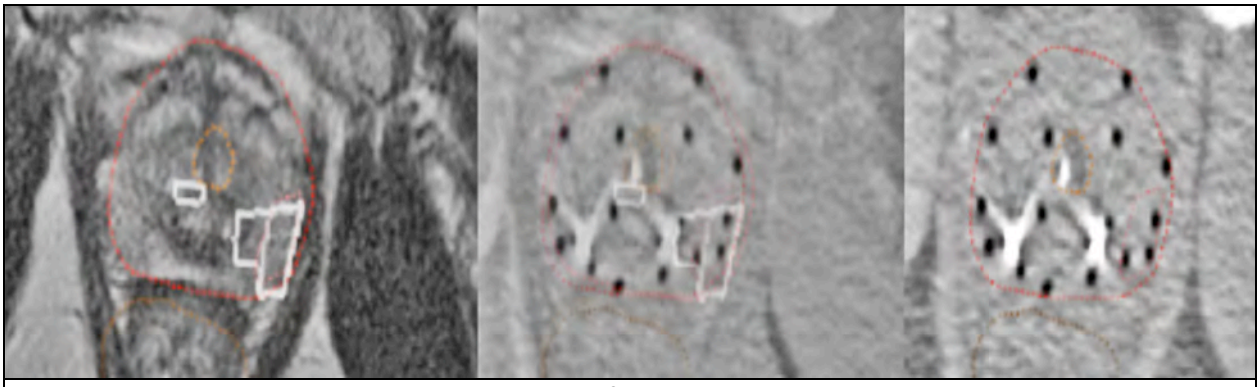

Figure 6: Adjusting transparency between MRI (left), MRI/CT 50-50 (center) and CT (right).

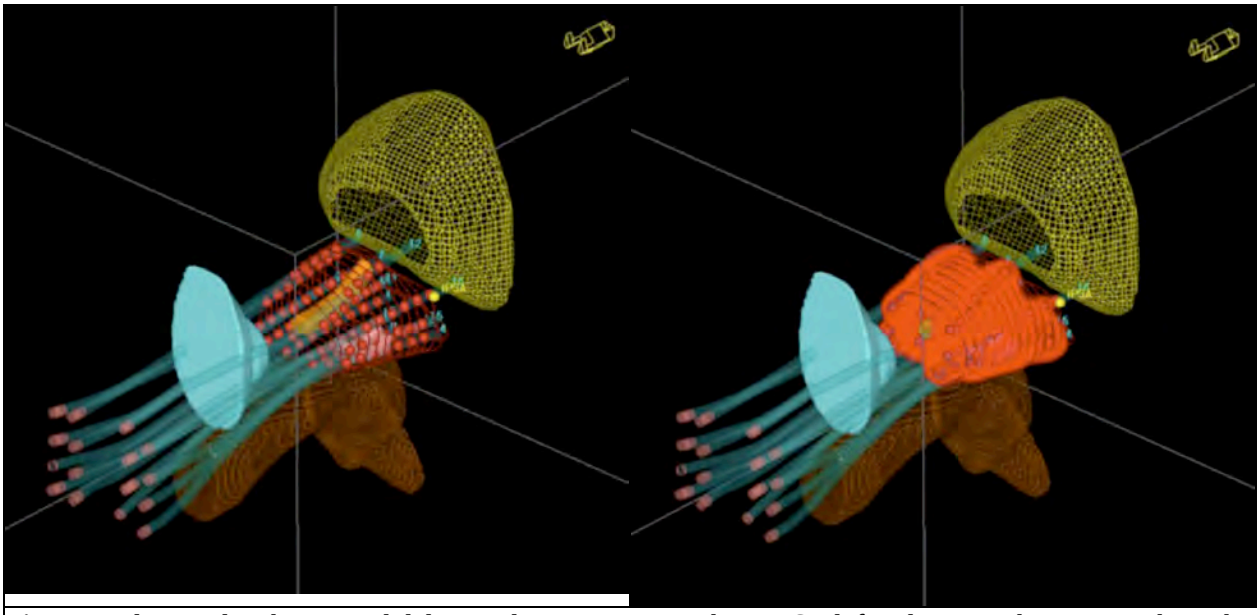

Figure 7: digitized catheters and delineated target organs. The MRSI-defined DIL is shown in pink on the left, and the right figure shows an isodose contour.

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